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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1804	

DATE MAILED: 02/10/97

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

See the attached Sheets.

Christopher S. F. Low

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800

PTO-90C (REV. 2/95)

1-File Copy

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Office Action Summary	Application No. 08/465,596	Applicant(s) Selden
	Examiner Christopher S. F. Low	Group Art Unit 1804

☒ Responsive to communication(s) filed on *29 October 1996 and 2 December 1996*.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-36 have been canceled and claims 37-71* is/are pending in the application.

Of the above, claim(s) *none* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *37-71* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

The amendment filed 29 October 1996 which canceled claims 1-35 and presented new claim 36 has been entered. It is also noted that on 2 December 1996, a supplemental amendment canceling claim 36 and adding new claims 37-71 was presented for examination. In view of the above indicated amendments, the following are or remain applicable to the pending claims.

35 U.S.C. 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 69-71 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The implants as claimed are implants as found in the animal or human. Note the comprises terminology in claim 33 results in the inclusion of the entire animal or human which contains the implant. Thus, the claims include within their scope a human (or other animal) and all of the cells in a human (or other animal). Thus, these claims do not constitute patentable subject matter because a claim (or claims) to the implant comprising is directed to or includes within its scope a human being and is not be considered patentable subject matter under 35 U.S.C. 101. See *American Wood v. Fiber Disintegrating Co.*, 90 U. S. 566 (1974); *American Fruit Growers v. Brogdex Co.*, 283 U. S. 1 (1931); *Funk Brothers Seed Co. v. Kalo Inoculant*, 33 U. S. 127 (1948); and *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). Insofar as claims 33-35 include within their scope a human being containing the implant, a human is not patentable subject matter because the limited but exclusive property right in a human being is barred by the United States Constitution. See 1077 OG 24. Note the absence of recitation of purified and isolated in the claims.

The non-statutory double patenting rejection, whether of the obvious-type or non-obvious-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (b) and (c) may be used to overcome actual or provisional rejection(s) based on non-statutory double patenting ground(s) of rejection set forth below provided the conflicting application(s) or patent(s) is/are shown to be commonly owned with this application. See 37 CFR 1.78 (d).

Effective January 1, 1994, a registered attorney or agent of record may sign a Terminal Disclaimer. A Terminal Disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 37-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the pending claims in copending application Serial No. 08/465,582. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are an obvious variation of the claims in the pending '582 application since in each application but in different words, the sets of claims recite implanting a transformed cell to produce an effect in a human, i.e., *in vivo* therapy which implants a cell or cells but which cells have, *ex vivo*, been transformed prior to implantation. The present claims also do not define over the interference count. Regardless of the vector, viral or nonviral and which in this instance, the vectors are obvious variations of effecting gene transfer into the implanted cells, the process of therapy and the intended end result is the same.

As to the above indicated rejection, applicant requests suspension in the 2 December 1996 response. Suspension does not *per se* resolve the issue of obviousness type double patenting nor does it present reasons for a different patentable invention.

Claims 37-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over pending claims 37-74 in copending application Serial No. 08/461,292 and over pending claims 37-71 in copending application Serial No. 08/460,902. Each of the three applications contain claims to processes of implanting transformed cells where the transformed cells express DNA that was inserted into the cells prior to implantation. Here, altering the concentration of a gene product is the same as expressing the gene to produce a product in the '292 application and of putting those cells which express the gene into a host as in the '902 application.

Claims 37-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 135-161 of copending application serial no. 08/334,797 which is a FWC of 07/787,840 in view of Salser *et al.* (US '796). Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed implants of transformed cells are not distinguishable from the cells set forth in the above claims of the copending application Both application claim transformed cells where the cells in the copending application are obvious variations of the cells claimed in the present implants wherein from the disclosure of the Salser *et al.* patent it would have been obvious to implant the genetically altered cells disclosed in the copending application which would have been the implants and process as presently claimed. Note that the copending application also claims a method of using the cells by maintaining the cells under conditions suitable for expression wherein the process disclosed in the present application claims is a process the keeps the cells in conditions suitable for expression of the DNA. Thus, the two applications claim the same inventive concept.

Claims 37-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 108-132 of copending application serial no. 08/334,455 which is a FWC of 07/911,533 in view of Salser *et al.* (US '796). Although the conflicting claims are not identical, they are not patentably distinct from each other because the presently claimed implants of transformed cells are not distinguishable from the cells set forth in the above claims of the copending application Both application claim transformed cells where the cells in the copending application are obvious variations of the cells claimed in the present implants wherein from the disclosure of the Salser *et al.* patent it would have been obvious to implant the genetically altered cells disclosed in the copending application which would have been the implants and process as presently claimed. Note that the copending application also claims a method of using the cells by maintaining the cells under conditions suitable for expression wherein the process disclosed in the present application claims is a process the keeps the cells in conditions suitable for expression of the DNA. Therefore, the two applications claim the same inventive concept.

Claims 37-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 108-132 of copending application serial no. 08/451,894. Although the claims are not identical, each set of claims recite providing a genetically altered cell to a mammal (copending application) or to a recipient subject (present application) each of which is the same set of animals. Therefore, the two applications claim the same inventive concept.

Claims 37-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 68-77 and 105-107 of copending application serial no. 08/446,909. Although the claims are not identical, each set of claims recite providing a genetically altered cell (in the copending application, the DNA encoding erythropoietin is a desired gene such as recited in the present application claims) to a mammal (copending application) or to a recipient subject (present application) each of which is the same set of animals. Therefore, the two applications claim the same inventive concept.

Claims 37-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 125-134 of copending application serial no. 08/446,912. Although the claims are not identical, each set of claims recite providing a genetically altered cell (in the copending application, the DNA encodes a glucagon-like peptide 1 is a desired gene such as recited in the present application claims) to a mammal (copending application) or to a recipient subject (present application) each of which is the same set of animals. Therefore, the two applications claim the same inventive concept.

Claims 37-71 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over at least claims 125-134 of copending application serial no. 08/443,936. Although the claims are not identical, each set of claims recite providing a genetically altered cell (in the copending application, the DNA encodes a therapeutic peptide is a desired gene such as recited in the present application claims) to a mammal (copending application) or to a recipient subject (present application) each of which is the same set of animals. Therefore, the two applications claim the same inventive concept.

The above are *provisional* obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-71 are rejected under 35 U.S.C. 112, first paragraph, because the written description inadequate and does not enable the claims. It does not reasonably provide written description and enablement for all animals and all genes since it does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to apply the teachings in the application to all animals and all genes so as to be commensurate in scope with these claims.

The written description does not demonstrate the process with all classes of animals and genes which are included by generic recitation in the claims. The "recipient subject" as broadly recited includes plants as well as animals. However, (page 15 of the specification) to read animal into the claims is improper and the specification does not disclose how to extrapolate from the lone use of mice without undue experimentation to all animals. It is noted that mice have in some instances been used as an animal model but extrapolations and generalizations based upon mice as applied to primates, such as humans do not always work due to the biological and functional differences between the different species such that here, where gene therapy is involved and all of the specific factors involved in making transfected cells or even hybridomas have not been determined as evidenced by the low rate of reproducibility as examined as of the time the claimed invention was made. In this regard, EXAMPLE 6 and 7 of the specification show that even in mice, there is an interaction of the transplanted cells and the mouse immune system as well as the necessity of suppression of the immune system to prolong the life of the implants (none of which are in the claims). Thus, applicants invention is not enabled as set forth in the claims, i.e., no immunosuppression and or a loss of function in or of the transplanted cells *per se*. It presents an example untenable for general use with other animal species (see EXAMPLE 9 where immunodeficient nude mice are used) such that applicant is

queried as to where is it expected natural populations of equivalents of nude mice such as the remaining approximately 4500 mammalian species even exist (See Baker *et al.*) or is immunosuppresive therapy or thymectomy to be universally applied to all animals subjected to the presently claimed method of therapy? See also the Cline (Am. J. Med.) reference at page 295 which indicates that of mice, dogs, sheep, primates (note humans are in same category as primates) only mice have shown consistent expression. EXAMPLE 10 shows one method of treating diabetes, but it clearly does not show or enable treating a disease where the receptor is either missing, defective, or present at a very reduced number on the cell surface, e.g. the instance where the insulin receptor is missing, defective, or present only at a much lower than normal level is apparently not ameliorated by the claimed method where more insulin would have been provided or how the number of insulin receptors per cell would have been regulated by the implanted transformed cells (see the Selden reference where it is disclosed that the mice died). Thus, the present genetic constructs, cells, and method face as broadly claimed, enormous genetic and physiological barriers as generalizations and extrapolations based upon one example using a mouse is not sufficient support for numerous regulatory sequences, variations in the genetic constructs, and claimed method where the Cline reference states that major hurdles still remain.

As to immunosuppression and the use of thymectomized mice, it does not show that the process successfully avoids the necessity of immunosuppression therapy to prolong the life of the implants. As to transient cytokine expression limited by effective immune response as useful, antibodies to a cytokine e.g., GM-CSF) produced by the recipient would have been expected to have the adverse effect of cross reacting with the host's own GM-CSF. What happens when transformed autologous cells are implanted into a host having a heterologous bone marrow transplant? Are there graft (heterologous bone marrow transplant) versus host (transformed autologous cell) reactions? The metes and bounds of the terminology used in the instant claims includes for example, insulin, and insulin for controlling diabetes is a desired product as well as one of any method of altering the concentration of any desired gene product wherein insulin is a gene product where the Selden reference indicates that mice so treated all died of hypoglycemia. The written description is inadequate and not enabled as directed to all recipient subjects (including humans, the intended recipients) since it does not demonstrate nor describe how to apply the teachings from the examples to humans with any

expectation of success especially where the Orkin *et al.* 7 December 1995 "REPORT AND RECOMMENDATIONS OF THE PANEL TO ASSESS THE NIH INVESTMENT IN RESEARCH ON GENE THERAPY". The report is indicative that there has been no demonstration of clinical efficacy in any gene therapy protocol despite anecdotal claims of success. Insofar as this is the case in 1995, it is not seen that in 1987, some eight years earlier, that any form of therapy was adequately described nor is it enabled. From the foregoing, indicated failures and failure in the present application, one is not led to practice the claimed invention with any expected success.

The controlling decision in the chemical enablement area is deemed to be *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971) where the court held that "... there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim ...". See also *Ex parte Hitzeman*, 9 USPQ2d 1821 (PTO Bd. Pat. Appl. Int., 1988), where more than a single example is required in unpredictable cases where recombinant DNA genetic actions and gene therapy are unpredictable fields of endeavor. Here, where all of the factors affecting recombinant DNA gene expression in mammalian cells have not been completely elucidated are coupled to selective gene/cell transplantation and where transient expression has only been shown in one animal, the mouse (in this application) and only transiently in dogs, sheep, and primates, it is clear that adequate written description that enables is not present for the broad claims presently rejected. Clearly the present situation ranks in the arena of enabling doubt to which the *Marzocchi et al.* and *Hitzeman* decisions speak.

Here, not only are the instant genetic inventions more prone to unpredictability and thus, less likely to enable related genetic constructions of hybrid cells much less a modified multicellular organism but also the meager scope of the instant application does not address the vagaries of the differences between the species of organisms that affect expression of the inserted genetic material or provide a reasonable discussion of how one of ordinary skill in the art would have resolved those differences such that practicing the claimed invention would have resulted in obtaining the stated results in all animals using all genes and all types of cells. Thus, the specification does not reasonably correlate with the claims as cautioned by *In re Fisher*, 166 USPQ 18 and in *Ex parte Hitzeman*,

9 USPQ2d 1821 (PTO Bd. Pat. Appl. Int., 1988). It was stated that a single embodiment may provide broad enablement involving predictable factors. Here, all of the factors involved in transplant rejection and host immunosuppression *per se* have not been set forth, determined, or even how these factors interact with each other in all animals, more is required as this case involves unpredictable factors. See *In re Angstadt*, 190 USPQ 213 (CCPA 1976), where it was pointed out that while applicants are not required to disclose every claimed species encompassed by the claims, each case, especially in unpredictable arts, must be determined on its own facts for determining the adequacy of Section 112. It was further pointed out that in many chemical (and biochemical) processes, and catalytic processes, particularly, are unpredictable (as would be the genetic constructs, hybrid cells and multicellular animals containing these cells and/or genetic constructs). Thus, here, the scope of enablement varies inversely with the degree of unpredictability of the factors involved. Note that the Selden *et al.* reference (New Eng. J. Med.) which is authored by applicant (page 1075) indicates that serum glucose levels fell in mice containing the implants and ultimately died of transkaryotic implantation-induced hypoglycemia. This statement by applicant demonstrates the unpredictability and inability to provide the appropriate ability in the implanted cells to regulate the levels of the expressed gene, even in mice (note that even at a point in time after the invention was made, Robinson (page 155) indicated that performance *in vivo* is the ultimate test of any system and appropriate animal models are important for developing such protocols where here, the Selden reference demonstrates the inability to regulate performance *in vivo*). Here, the Crystal reference points out that results are often inconsistent and that for extrapolation from mice to humans, humans are not large mice as the predictions of gene transfer studies in experimental animals have not been borne out in human trials (see page 409). Each of the foregoing creates doubt and an undue amount of experimentation in view because of unpredictability in the state of the art at and after the time the claimed invention was made.

Claims 37-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 37 is indefinite as to claim 47 since claim 37 requires effecting gene expression (i.e., increasing the amount of a gene product) as opposed to claim 47 which requires a decrease in the amount of that gene product. Claim 44 is indefinite as to what is "an equivalent to a native gene" since

the added gene is new to the subject, it is unclear what it would be equivalent to. Claim 56 is indefinite absent antecedent basis in claim 55 for the recitation of "said biological molecule" in claim 56.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

> A person shall be entitled to a patent unless
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 65, 66 and 69-71 are rejected under 35 U.S.C. 102 (b) as being anticipated by any of the dozens of commercial monoclonal antibodies and hybridomas producing them. The compositions as claimed are the same despite their manner of production. The method does not impart any different characteristics or properties.

Claims 37, 38, 40 43, 44, 46, 49, 50, 52, 53, 55, 56, and 69 are rejected under 35 U.S.C. 102 (b) as being anticipated by the Rosenberg patent (US '893) which discloses transforming cells to produce a desired gene product which is insulin (see at least the abstract, col 2 and 6) and selecting cells that are temperature sensitive for insulin secretion (col 6-7), i.e., regulated. The insulin producing cells are for implantation (col 8+). Expression of insulin from the transformed cells alters the concentration of the gene product, and, when in mice that do not produce insulin (diabetic mice), the transformed cells produce a product not previously expressed and which product is equivalent to a native gene.

Claims 37-39, 41, 43-45, 49, 50, 52, 65, 66, and 69-71 are rejected under 35 U.S.C. 102 (b) as being anticipated by Goding who disclose growth of hybridomas in animals where the concentration of the desired product (antibody) and the intraperitoneally injected hybridoma cells are transformed cells containing heterologous DNA from different cells and which cells produce antibody that is specific to an antigen. The location into which the cells are transplanted does not alter the cells.

Claims 37-39, 41, 43-50, 53, 55, and 69-71 are rejected under 35 U.S.C. 102 (b) as being anticipated by Williams *et al.* (Nature) who disclosed altering the concentration a desired gene product by using a retrovirus to transfect pluripotent hematopoietic stem cells and transplanting same back into the host animal (see at least the abstract) where the gene conferring G418 resistance was expressed. Insofar as the animals were irradiated and the transplanted cells restored functions lost due to irradiation, the transplanted cells provided for the return to expression of genes and gene functions equivalent to native genes of the recipient as well as a gene product not previously expressed by the recipient. Note that irradiation effected the loss of expression of desired gene products and the implantation of the transfected cells compensated for the loss of expression by providing equivalent gene functions expressed in the implanted transfected cells. The location into which the cells are transplanted does not alter the cells.

Claims 37-39, 41, 43, 44, 49, 50, 53, 55, and 69-71 are rejected under 35 U.S.C. 102 (b) as being anticipated by Miller *et al.* (Science) who disclosed altering the concentration a desired gene product by using a retrovirus to transfect pluripotent hematopoietic stem cells and transplanting same back into the host animal (see at least the abstract). Lesch-Nyhan syndrome (page 631-623) is caused by a defect in the gene encoding human hypoxanthine phosphoribosyltransferase (HPRT) expressed in mice and the gene product is equivalent to the mouse HPRT (note the dimer formation at page 631) and the location into which the cells are transplanted does not *per se* alter the cells.

Claims 37-56 and 69-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopchick *et al.* (EPO '640) taken with Salser *et al.* (US '796), Anderson (Science), and Williams *et al.* (Nature).

Kopchick *et al.* disclosed recombinant DNA constructs for expression of growth hormone from transfected cells encapsulated in hollow fibers and implanted into animals where the reference indicated that "... other cell lines producing other proteins can be encapsulated in these fibers and used as herein described and that any eukaryotic cell can be transfected ..." (see page 12). Thus, it would have been anticipated if not obvious that not only are mouse cells used but that cells for example from "animal species. This would have motivated one of ordinary skill in the art to use other cells and animals such as those described in the Salser *et al.* reference which disclosed transferring genes to intact mammals via cells genetically altered to contain modified genes (a wide variety of genes, col 2). The cells were reintroduced into the mammal and directed, via the gene construct(s), expression of the exogenous DNA (see at least col 3+). See at least the abstract and the claims. Here, where Salser *et al.* do not explicitly indicate a promoter type (col 4-5), one of ordinary skill in the art would have nevertheless found it obvious to combine the Kopchick *et al.*, Salser *et al.* and Anderson references since Salser *et al.* indicated obtaining expression and Anderson disclosed (page 405+) that various types of expression control DNA were known and had been used to regulate expression. It would have also been obvious to anyone of ordinary skill in the art that autologous cells would have minimized adverse immunological effects of the implanted cells in the host animal.

One of ordinary skill in the art would also have combined the Kopchick *et al.*, Salser *et al.* and Anderson teachings with that of the Williams *et al.* (Nature) reference because this reference like the Salser *et al.* and Anderson references disclosed altering the concentration a desired gene product by using a retrovirus to transfect pluripotent hematopoietic stem cells and transplanting same back into the host animal (see at least the abstract) where the gene conferring G418 resistance was expressed. Insofar as the animals were irradiated and the transplanted cells restored functions lost due to irradiation, the transplanted cells provided for the return to expression of genes and gene functions equivalent to native genes of the recipient as well as a gene product not previously expressed by the recipient. Note that irradiation effected the loss of expression of desired gene products and the implantation of the transfected cells compensated for the loss of expression by providing equivalent gene functions expressed in the implanted transfected cells. The location into which the cells are

transplanted does not alter the cells. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 57-66 and 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kopchick *et al.* (EPO '640) taken with Salser *et al.* (US '796), Anderson *et al.* (Science), and Williams *et al.* as applied to claims 37-56 and 69-71 above, and further in view of Sevier *et al.* (Clin. Chem.).

Kopchick *et al.*, Salser *et al.*, Anderson, and Williams *et al.* are applied here as indicated above and disclosed providing somatic cell gene transfer to animals where the gene(s) are expressed. Sevier *et al.* teach using immunoassays to assay for a wide variety of biological products. It would have been obvious to one of ordinary skill in the art to have measured the gene product(s) such as indicated in the Kopchick *et al.*, Salser *et al.*, Anderson, and Williams *et al.* references by conventional immunoassays known to measure expression and the effectiveness of the treatment. It would also have been known to the skilled artisan that proteins foreign to the host animal are antigenic. The Williams *et al.* reference minimizes the problem via lethal irradiation of the animal and have antibodies thereto where the Sevier *et al.* reference discloses antibodies produced in response to an antigen. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claim 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Kopchick *et al.* (EPO '640) taken with Salser *et al.* (US '796), Anderson *et al.* (Science), and Williams *et al.* as applied to claims 37-56 and 69-71 above, and further in view of Lindstrom (US RE 30,059).

Kopchick *et al.*, Salser *et al.*, Anderson, and Williams *et al.* are applied here as indicated above and disclosed providing somatic cell gene transfer to animals where the gene(s) are expressed and show the host animal. Here, Lindstrom teaches measuring antibody as a measure of immunosuppression induced by the treatment. See column 4, Table 1 and column 1, lines 28-30. It would be obvious to use the Lindstrom assay to assess in the patient, the treatment efficacy of suppressing antibody production. It would have been obvious one of ordinary skill in the art to apply the Lindstrom assay to other animals, such as those treated in the primary references to measure the

effects of nonspecific immunosuppressive agents. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). Applicant's present claims are admitted in the response as identical to original claims 1-35 which were rejected. Said rejections are repeated above.

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Low whose telephone number is (703) 308-2923. Inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1) and must conform to the notice published in the Official Gazette, 1096 OG 30 (15 November 1989). The telephone number assigned to Art Unit 1804 in the CM1 PTO Fax Center is (703) 308-4312.

CSFL
5 February 1997

CHRISTOPHER S. F. LOW
PRIMARY EXAMINER
GROUP 1800